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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/764,141	01/19/2001	Peter N. Devreotes	01107.00060	8190
22907	7590	11/24/2004	EXAMINER	
BANNER & WITCOFF 1001 G STREET N W SUITE 1100 WASHINGTON, DC 20001			CHANDRA, GYAN	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/764,141

Applicant(s)

DEVREOTES ET AL.

Examiner

Gyan Chandra

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 01 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-93 is/are pending in the application.
- 4a) Of the above claim(s) 1-10, 11, 26-55 and 57-76 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11, 13-25, 56 and 77-93 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

The amendment filed on 09/01/04 has been entered.

Claims 1-10, 12, 26-55 and 57-76 were cancelled. Claims 11, 14-19, 24, and 56 were amended. Claims 11, 13-25, 56, 77-93 are pending and under examination.

Applicants' correction of objection of claims 11 and 56 removing nonelected subject matter is noted.

The objection to the specification for a new title is withdrawn pursuant to Applicants' acceptance of the suggested title. The title "Heterotrimeric G-protein" has been made of record.

### ***Claim Rejections - 35 USC § 112, first paragraph***

The rejection of claims 11-25, 56, 57 under **35 USC § 112**, first paragraph is withdrawn fully pursuant to Applicants' argument and evidence, which were persuasive.

### **New Grounds of Rejection:**

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 79-86, 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 79, 81, 84 and 85 read on luminescent protein as Cyan fluorescent protein. Cyan fluorescent protein is not a luminescent

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protein. Claims 80, 82, 83, and 86 read on luminescent protein as Yellow fluorescent protein. Yellow fluorescent protein is not a luminescent protein. Claims 83, 84, 85, 86 and 91 read on fluorescent protein as a light emitting luciferase protein. Luciferase protein is not a fluorescent protein. Since the specific embodiments of the claimed proteins appear to be contradictory, it is unclear what is encompassed within the claims and thus, the claims are indefinite.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 14-19, 21,22,25 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyaki et.al. (Nature 388: 882-887,1997) in view of Tian et.al. (Mol. Biol. Cell 9:2949-2961,1998).

The claimed invention is drawn to a functional heterotrimeric G protein comprising an  $\alpha$  subunit comprising a first amino acid sequence encoding a first fluorescent protein and a  $\beta$  subunit comprising a second amino acid sequence encoding a second fluorescent protein, wherein said first and second fluorescent proteins are capable of fluorescence resonance energy transfer (FRET).

Miyaki et.al. teach making genetic constructs of GFP and its variants (yellow or cyan fluorescent proteins) as fluorescent donor and acceptor proteins for use in studying intra and intermolecular interactions. They teach that making a tandem fusion of a fluorescent donor protein on one end of the study protein and fluorescent acceptor protein on the other end of the study protein enables studying ligand induced changes in the protein (page 883, line 1-4). Miyaki et.al. further teach that making a fusion with a fluorescent donor protein and a first protein, with fluorescent acceptor and a second protein, aids in visualizing cellular dynamics (FRET, see, page 886, second paragraph, line 23-24). Miyaki et.al. do not teach the application of FRET for studying heterotrimeric G proteins.

Tian et.al. teach that heterotrimeric G proteins play an important role in carrying cellular responses to external stimuli, such as hormones, neurotransmitters, light, odorants and chemoattractants (page 2949, introduction line 1-5). They teach that G  $\beta$  interacts with G $\alpha$  and G $\gamma$  to form a heterotrimeric complex and that G $\beta\gamma$  exists as a

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tight heterodimer. Tian et.al. also teach that  $G\alpha$  and  $G\beta$  interact with each other during signal transduction processes and that this interaction is required for cellular responses to hormonal and chemical stimuli to be carried out.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to genetically attach a fluorescent donor protein such as cyan with the  $G\alpha$  protein and a fluorescent acceptor protein such as YFP to the N-terminus of the  $G\beta$  protein or conversely, a fluorescent donor protein such as cyan with the  $G\beta$  protein and a fluorescent acceptor protein such as YFP to the N-terminus of the  $G\alpha$  protein using the method taught by Miyaki et al. The person of ordinary skill in the art would have been motivated do so to study the nature of the interactions between the  $G\alpha$  and  $G\beta$  proteins in response to various hormonal or sensory signals as taught by Tian et al.

Claims 13, 77-86, 89, and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyaki et.al. in view of Tian et.al. and further in view of Xu et.al. (Proc. Natl. Acad. Sci. USA 96: 151-156,1999).

The claimed invention is drawn to a heterotrimeric G protein wherein the first and second chimeric proteins are within 100 angstroms of each other, and where the first amino acid sequence encodes a first fluorescent or luminescent protein and the second amino acid sequence encodes a second fluorescent or bioluminescent protein, wherein the first and second fluorescent or luminescent proteins are capable of either FRET or luminescence resonance energy transfer (BRET).

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Miyaki et.al. and Tian et.al. do not teach that FRET and BRET can be used interchangeably and do not teach the optional distance between the fluorescent donor and the fluorescent acceptor proteins in order for FRET or BRET.

Xu et.al. teach that fluorescence resonance energy transfer efficiency is dependent on spectral overlap, the relative orientation and the distance between the donor and acceptor fluorophores. Xu et.al. teach that FRET works well when the distance between the first protein (fluorescent donor) and the second protein (fluorescent acceptor) is between 10 and 100 angstroms (page 151, first column, line 30-34). Xu et.al. also teach that fluorescent and bioluminescent proteins may be used interchangeably in FRET and BRET (see page 153, second column, line 11-17 of the second paragraph) and further teach that BRET does not require excitation illumination in contrast to FRET and thus, offers advantages for its use in photo-responsive cells (see, page 154, first column, 2<sup>nd</sup> paragraph).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to attach the fluorescent donor and acceptor proteins taught by Miyaki et.al. in view of Tian et.al. within a distance of 100 angstroms. The person of ordinary skill in the art would have been motivated to use FRET and BRET interchangeably because Xu et.al. teach that the optional distance for FRET is within 100 angstroms and the use of BRET over FRET offers advantages in photo-responsive cells.

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Claims 20, 23-24, 87-88, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyaki et.al. in view of Tian et.al., and further in view of Medina et.al. (J. Biol. Chem. 271: 24720-24727, 1996) and Wall et.al. (Cell 83:1047-1058, 1995).

Claims 20, 23-24, 87-88, and 90 are drawn to a functional heterotrimeric G protein comprising first and second fluorescent proteins capable of FRET, wherein the first amino acid sequence is within a helical domain of  $G\alpha$  protein a subunit, and the second amino acid sequence is at the N-terminus of the  $\beta$  subunit.

Miyaki in view of Tian et.al. teach a functional heterotrimeric G protein with first and second fluorescent fusion proteins capable of FRET as set forth supra. Neither Miyaki et.al. nor Tian et.al. teach attaching first fluorescent protein (donor) in the helical domain of  $G\alpha$  protein and the second fluorescent protein (acceptor) to the N-terminus of the  $G\beta$  protein.

Medina et.al. teach that the N-terminus (amino acid 1-56) and C-terminus (amino acid 182-356) are important for  $G\alpha$  protein function (see, page 24725, line 5) and also teach that replacing the amino acids 57-181 of  $G\alpha$  with homologous  $\alpha_2$  residues retained  $G\alpha$  protein functions.

Wall et.al. teach that the amino and carboxyl termini are important for G protein heterotrimeric function. Wall et.al. teach that the first 33 N-terminus amino acids of  $G\alpha$  are crucial for G protein heterotrimer complex formation and deletion of N-terminus of  $G\alpha$  prevents association with  $G\beta$  (see page, 1054, 2<sup>nd</sup> paragraph). This leads into  $G\alpha$  helices, after the amino acid 57, a point of attachment for a fluorescent or bioluminescent protein with the first protein. Wall et.al. further teach that the binding between  $G\beta$  and



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G $\gamma$  subunit is of very high affinity and that the subunits can be separated only by denaturants (page 1047, second column, line 8-12). They teach that the N-terminus of G $\beta$  is open and forms an extended helical polypeptide chain pointing towards the N-terminus of G $\alpha$  protein (see page 1052, 1<sup>st</sup> column, 3<sup>rd</sup> paragraph). This renders N-terminus of the second protein (G $\beta$ ) an obvious point for the attachment of a fluorescent or bioluminescent protein.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to attach a fluorescent donor protein such as cyan within the helical loop of the first protein after the amino acid residue 56 as taught by Wall et.al. and Medina et.al., and a fluorescent acceptor protein such as YFP to the N-terminus of the second protein for FRET as taught by Wall et al.

### ***Conclusion***

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra  
AU 1646  
26 October 2004

  
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